REMARKS

Claims 34-37, 42-45, 66-69, 77, and 80-91 are pending in the application. Claims 80-84 are withdrawn as being drawn to non-elected inventions. New claims 89-91 have been added. Claims 34-37, 42-45, 66-69, 77, and 85-88 are under active consideration.

Claims 34, 37, 42, 45, 66, 69, 77, 85, and 88 have been amended to recite nucleic acids encoding immunogenic polypeptides or fusion proteins comprising native HCV epitopes. Support for the amendments can be found in the specification, for example, at page 11, line 22 through page 12, line 2; page 22, lines 25-26; page 26, lines 27-29.

Support for new claims 89-91 can be found in the specification, for example, at page 26, lines 27-30 and page 29, lines 23-25.

Amendment of the claims is made without prejudice, without intent to abandon any originally claimed subject matter, and without intent to acquiesce in any rejection of record. Applicants expressly reserve the right to file one or more continuing applications hereof containing the canceled or unamended claims.

Applicants note with appreciation the withdrawal of the previous rejection under 35 U.S.C. § 112, second paragraph.

35 U.S.C. § 112, first paragraph, Written Description

Claims 34, 35, 37, 42, 43, 45, 66, 67, 69, 77, and 85-88 remain rejected under 35 U.S.C. § 112, first paragraph, for alleged lack of an adequate written description.

The Office Action alleges that the claims lack "sufficient written description support for nucleotides encoding the genus of peptides comprising immunogenic sequences having at least about 90% identity to an HCV sequence" (Office Action, page 3). In particular, the Office Action asserts that the previous amendment setting forth the limitation that such sequences comprise an HCV epitope was insufficient to overcome the rejection because the application defines an epitope as including "sequences identical to the native sequence as well as modifications to the native sequence, such as deletions, additions, and substitutions" (Office Action, page 3). Applicants respectfully traverse the rejection under 35 U.S.C. § 112 first paragraph for the reasons previously made of record in the response to the Office Action of January 13, 2006 and on the following grounds.

Applicants respectfully submit that the current claims indeed comply with the written description requirement of 35 U.S.C. § 112, first paragraph. In particular, claims 34, 37, 42, 45, 66, 69, 77, 85, and 88 have been amended to recite that the nucleic acids encode an immunogenic polypeptide or fusion protein comprising a native HCV epitope. The Examiner has acknowledged that sequences encoding native HCV epitopes do satisfy the written description requirement (see, *e.g.*, Office Action, page 3).

Therefore, withdrawal of the written description rejection under 35 U.S.C. § 112, first paragraph, is respectfully requested.

35 U.S.C. § 103

A. Rejection based on Major in view of Michalak and Valenzuela

Claims 34-36, 42-44, and 66-68 remain rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over the reference of Major et al. (J. Virol. 69:5798-5805; hereinafter "Major") in view of the reference of Michalak et al. (J. Gen. Virol. 78:2299-2306; hereinafter "Michalak") and further in view of Valenzuela et al. (Bio/Technology 3:323-326; hereinafter "Valenzuela (1)").

In maintaining the rejection, the Office Action alleges that Applicant has not considered the teachings of the references cumulatively, or identified what limitations in the claims are not met by the combination of the references (Office Action, page 6). Applicants respectfully traverse the rejections under 35 U.S.C. § 103 and the Office Action remarks and purported facts underlying the rejection on the following grounds.

To support an obviousness rejection under 35 U.S.C. § 103, "all the claim limitations must be taught or suggested by the prior art." M.P.E.P. § 2143.03. In addition, "the teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure." M.P.E.P. § 706.02.

The claims are directed to nucleic acids encoding a fusion protein comprising a substantially complete S domain of HBsAg and (a) a polypeptide comprising amino acid

residues 384 to 661 of an HCV-1 polyprotein or (b) the corresponding amino acids of other HCV isolates or (c) a sequence having at least 90% identity to (a) or (b).

Applicants again emphasize that none of the cited references teach or suggest a nucleic acid encoding a fusion protein combining an HBsAg polypeptide and an E2 polypeptide, as claimed. On the contrary, the primary reference of Major teaches away from the claimed combination. Major does not recommend the use of E2 antigens because of data showing variability in the envelope regions, which Major concludes "bring into question the suitability of these antigens in immunization programs" (see page 5804, col. 1). Major instead teaches a nucleic acid encoding HBsAg and a portion of an HCV **core** antigen. In particular, Major states that the core region was chosen for incorporation into fusion proteins because it is "well conserved between genotypes" (see page 5798, col. 1). Since Major teaches away from the use of E2 antigens, Major cannot provide the motivation for combining the references as suggested by the Examiner.

Nor do any of the secondary references teach or suggest the claimed invention. Michalak describes truncated forms of HCV E1 and E2 **proteins** having C-terminal deletions. The focus of Michalak is on the biochemical characterization of truncated forms of E2 to determine the effect of C-terminal deletions on E2 secretion and protein folding. Nowhere does Michalak describe or suggest a **nucleic acid** encoding E1 or E2 antigens fused to any HBV sequence. Michalak cannot provide the requisite motivation to produce nucleic acids encoding fusions of HCV E2 with HBsAg, as claimed, because Michalak is silent as to fusions of E2 with any HBV antigen, let alone HBsAg. Furthermore, Michalak fails to describe any vaccines comprising nucleic acids encoding HCV or HBV antigens.

Valenzuela also fails to fill the gaps. Valenzuela does not describe or suggest immunization using HCV antigens. Rather, Valenzuela pertains to immunization against herpes simplex virus utilizing a vector expressing a hybrid particle comprising HBsAg and herpes simplex virus surface antigens. Valenzuela cannot provide the motivation to combine the references as suggested by the Examiner because Valenzuela is silent with regard to HCV fusions.

The Examiner's citation of M.P.E.P. § 2144.06 in support of the rejection is believed to represent a misapplication of the law. M.P.E.P. § 2144.06 states (emphasis added):

> It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be **useful for the same purpose**, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art.

As discussed above, Michalak does not describe any immunogenic compositions comprising nucleic acids encoding HCV or HBV antigens. On the contrary, Michalak describes the use of truncated E2 **polypeptides** in biochemical studies. Valenzuela also fails to describe any nucleic acids encoding HCV antigens for immunization against HCV. Therefore, the Examiner is combining compositions that are **not** taught to be useful for the same purpose.

It is the invention as a whole that is novel and nonobvious. In the absence of some teaching or suggestion in the cited references concerning nucleic acids encoding fusion proteins comprising a substantially complete S domain of HBsAg and a polypeptide comprising amino acid residues 384 to 661 of an HCV-1 polyprotein; as described in the present application, the Examiner has presented no more than an improper hindsight reconstruction of the present invention.

B. Rejection based on Jacobs in view of Major, Michalak, and Valenzuela

Claim 77 remains rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over the reference of Jacobs et al. (U.S. Patent No. 6,306,625; hereinafter "Jacobs") in view of Major et al., Michalak et al. and Valenzuela et al. as applied to claims 34-36, 42-44, and 66-68. Jacobs is cited for teaching the use of HBsAg as a carrier molecule for other antigenic sequences, the fusion of such antigenic sequences to the N-terminus of the S protein sequence, cell lines comprising nucleic acids encoding chimeric antigens in combination with nucleic acids encoding only HBsAg, and the production from such cell lines of HBsAg particles comprising chimeric antigens. In maintaining the rejection, the Office Action asserts that Applicants' previous traversal of

the rejection on the basis that Jacobs does not teach or suggest the fusion of HBsAg with an HCV antigen is not persuasive in view of the references of Major and Michalak. Applicants respectfully traverse the rejection under 35 U.S.C. § 103 and the remarks and purported facts underlying the rejection on the following grounds.

Claim 77 is directed to a cell line that expresses a virus-like particle (VLP) comprising a first HBsAg and a chimeric antigen, wherein the chimeric antigen comprises a second HBsAg which is linked to an immunogenic polypeptide, and wherein the first and the second HBsAg each comprise a substantially complete S domain, wherein said immunogenic polypeptide comprises (a) amino acid residues 384 to 661 of an HCV-1 polyprotein; or (b) the corresponding residues of other HCV isolates; or (c) a sequence having at least about 90% sequence identity to (a) or (b), wherein said polypeptide comprises an HCV epitope and is capable of eliciting an immunological response against HCV.

Applicants again point out that Jacobs fails to describe any cell line producing VLPs containing a chimeric antigen comprising an HCV immunogenic polypeptide. As discussed above, none of the references of Major, Michalak, and Valenzuela teach or suggest nucleic acids encoding a fusion combining, in particular, HBsAg and an E2 polypeptide. Moreover, none of the references teach a cell line expressing virus-like particles comprising HBsAg in addition to a chimeric antigen comprising HBsAg linked to an HCV immunogenic polypeptide. Therefore, no combination of the cited references teaches or suggests all the limitations of claim 77.

C. Rejection of the claims based on Jacobs in view of Major, Michalak, and Valenzuela, further in view of GenBank Accession Numbers X02763 and M62321

Claim 37 remains rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over the reference of Jacobs et al. in view of Major et al., Michalak et al. and Valenzuela et al. as applied to claim 77, and further in view of GenBank Accession Numbers X02763 and M62321. The Examiner asserts that the sequence of nucleotides 1564-2241 of X02763 corresponds to the sequence of nucleotides 2907-3583 of SEQ ID

NO:6, coding for HBsAg, and that the sequence of nucleotides 1491-2324 of M62321 corresponds to the sequence of nucleotides 2067-2900 of SEQ ID NO:6, coding for a portion of the HCV E2 protein. In maintaining the rejection, the Office Action asserts that Applicants' previous traversal of the rejection on the basis that the cited art provides no motivation to combine an HBsAg sequence with an HCV E2 sequence is not persuasive in view of the references of Major and Michalak. Applicants respectfully traverse the rejection under 35 U.S.C. § 103 and the remarks and purported facts underlying the rejection on the following grounds.

Claim 37 is directed to a nucleic acid molecule comprising nucleotides 1992 through 3584 of SEQ ID NO:6, or a nucleotide sequence having at least about 90% sequence identity thereto that is capable of expressing a fusion protein that comprises an HCV epitope and elicits an immunological response against HCV.

Applicants reiterate that no motivation can be found in any of the cited references for combining the two sequences of X02763 or M62321 to produce SEQ ID NO:6 as suggested by the Office Action. As discussed above, none of the cited references teach or suggest a nucleic acid encoding a fusion comprising HBsAg and an HCV E2 antigen. X02763 and M62321 do not disclose or suggest any construct encoding such a fusion. In particular, X02763 and M62321 fail to disclose or suggest the 75 nucleotides from 1992 to 2066 of SEQ ID NO:6 or the 6 nucleotides of SEQ ID NO:6 forming the "linker" between the end of the M62321 sequence and the beginning of the X02763 sequence. Contrary to the Examiner's assertions (Office Action, page 7), Michalak and Major do not make up for the difficiencies of X02763 and M62321 because neither Michalak nor Major teach or suggest nucleic acids encoding fusions combining HBsAg and E2 polypeptides, as claimed, and allusions to HCV antigens generally do not teach or suggest the specific claimed invention. Therefore, no combination of the cited references teaches or suggests all the limitations of claim 37.

D. Jacobs in view of Major, Michalak, and Valenzuela (1), further in view of De Wilde, Valenzuela (2), and Mountford

In addition, claims 85-87 remain rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over the reference of Jacobs et al. in view of Major et al., Michalak et al. and Valenzuela et al., as applied to claim 77, and further in view of the references of De Wilde et al. (U.S. Patent No. 5,928,902; hereinafter "De Wilde"), Valenzuela et al. (U.S. Patent No. 4,722,840; hereinafter "Valenzuela (2)"), and Mountford et al. (Proc. Natl. Acad. Sci. U.S.A. 91:4303-4307; hereinafter "Mountford"). De Wilde is cited for teaching that hybrid particles form between hybrid HBsAg proteins and native HBsAg protein when host cells are co-transformed with nucleic acids encoding both the native and the hybrid HBsAg proteins. Mountford is cited for teaching the use of a viral IRES to induce the expression of two proteins in the same transformation vector. In maintaining the rejection, the Office Action alleges:

> In view of the fact that Major is teaching the use of the HBsAg protein as a carrier for an anti-HCV antigen, and as the Michalak reference teaches an HCV antigen for use in the induction of an anti-HCV immune response (as described on pages 6-8 of the action mailed on July 29, 2005), those in art would have had sufficient motivation to combine these teaches to use the HBsAg protein as a carrier for the anti-HCV antigens of Michalak. Moreover, it is noted that in these references, both the HCV core (Major) and E2 proteins (Michalak) are identified as anti-HCV antigens. It would therefore have been prima facie obvious to substitute one of these antigens with the other. (Office Action, page 8.)

Applicants respectfully traverse the rejection under 35 U.S.C. § 103 and the remarks and purported facts underlying the rejection on the following grounds.

Claims 85-87 are directed to vectors comprising a nucleic acid sequence which encodes a first HBsAg and a nucleic acid sequence which encodes a fusion protein comprising a second HBsAg which is linked to an immunogenic polypeptide, wherein the first and the second HBsAg each comprise a substantially complete S domain; and wherein the immunogenic polypeptide comprises (a) amino acid residues 384 to 661 of an HCV-1 polyprotein; or (b) the corresponding residues of other HCV isolates; or (c) a sequence having at least about 90% sequence identity to (a) or (b), wherein said

polypeptide comprises an HCV epitope and is capable of eliciting an immunological response against HCV.

As discussed above, Major, Michalak, and Valenzuela (1) fail to teach or suggest any nucleic acid encoding a fusion protein comprising HBsAg and an HCV E2 antigen. Although the Examiner suggests that the solubility of the truncated E2 antigen taught by Michalak would provide the motivation to combine the references (Office Action, page 8), the solubility of E2 by itself is not obviously relevant to immunization with E2 fusion proteins contained in virus-like particles comprising HBsAg, as taught by the instant application. Thus, Michalak cannot provide the requisite motivation for combining the references as suggested by the Examiner. Nor does Major teach nucleic acids encoding fusions of HBsAg and E2, as discussed above. Furthermore, Major, Michalak, and Valenzuela (1) fail to teach or suggest a vector comprising a nucleic acid sequence which encodes HBsAg in addition to a nucleic acid sequence which encodes a fusion protein comprising HBsAg linked to an HCV immunogenic polypeptide.

De Wilde pertains to immunization against malaria infection, and accordingly, teaches a hybrid protein comprising the CS protein of *P. falciparum*. De Wilde fails, however, to teach any nucleic acid encoding a fusion of HBsAg to any HCV immunogenic polypeptide, nor does De Wilde provide any motivation for using any HCV antigen.

Valenzuela (2) similarly fails to disclose or suggest any nucleic acid or vector encoding a chimeric antigen comprising HBsAg linked to an HCV immunogenic polypeptide.

Mountford merely describes bicistronic constructs in general and has nothing to do with expression of HCV fusions or VLPs. Therefore, no combination of the cited references teaches or suggests all the limitations of claims 85-87.

E. Jacobs in view of Major, Michalak, and Valenzuela (1), further in view of De Wilde, Valenzuela (2), and Mountford, further in view of GenBank Accession Numbers X02763 and M62321

In addition, claim 88 has been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over the reference of Jacobs et al. in view of Major et al., Michalak et al. and Valenzuela (1) et al., further in view of the references of De Wilde et al. Valenzuela (2) et al., and Mountford et al., as applied to claims 85-87, further in view of the references of GenBank Accession Numbers X02763 and M62321, as applied to claim 37. In particular, the Office Action alleges that "each of the limitations of this claim is met by the teachings of the combined references" (Office Action, page 9). Applicants respectfully traverse the rejection under 35 U.S.C. § 103 and the remarks and purported facts underlying the rejection on the following grounds.

Claim 88 is drawn to the vector of claim 85 comprising the nucleotide sequence of SEQ ID NO:6, or a nucleotide sequence having at least about 90% sequence identity to the sequence of SEQ ID NO:6, wherein the vector is capable of expressing a fusion protein that comprises a native HCV epitope and elicits an immunological response against HCV.

None of the cited reference teach a vector comprising SEQ ID NO:6, as claimed. As discussed above, Major, Michalak, and Valenzuela (1) fail to teach or suggest a vector comprising a nucleic acid sequence which encodes HBsAg in addition to a nucleic acid sequence which encodes a fusion protein comprising HBsAg linked to an HCV immunogenic polypeptide. De Wilde, Valenzuela (2), and Mountford fail to teach or suggest any nucleic acid encoding a fusion of HBsAg to an HCV E2 polypeptide, nor provide any motivation for using any HCV antigen. Furthermore, the GenBank entries of X02763 and M62321 fail to provide any motivation for combining the sequences of HBsAg and E2 in the manner of the instant invention.

F. No Motivation for Combining the References

The Examiner cannot point to anything in any of the cited references that provides the motivation for reproducing the claimed invention. It is axiomatic that statements in

the prior art must be considered in the context of the teaching of the entire reference, and that rejection of claims **cannot** be predicated on mere identification in a reference of individual components of claimed limitations. In this regard, the Federal Circuit has consistently reversed a finding of obviousness, even when all claimed elements are individually present in the references. *See, e.g., In re Kotzab* 217 F.3d 1365, 55 USPQ2d 1313, 1317 (CAFC 2000).

Without a suggestion to modify the references evident in the prior art, as well as a lack of a reasonable expectation of success, the only conclusion supported by the record is that the rejection was made impermissibly using hindsight reconstruction of the invention. As stated by the Court of Appeals for the Federal Circuit, "[i]t is impermissible to use the claimed invention as an instruction manual or 'template' to piece together the teachings of the prior art so that the claimed invention is rendered obvious." *In re Fritch*, 23 USPQ2d 1780, 1784 (Fed. Cir. 1992). As also stated by the Court of Appeals for the Federal Circuit "One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention." *In re Fine*, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988). Therefore, the Office has not met the requirements for a *prima facie* showing of obviousness under 35 U.S.C. § 103.

For at least the above reasons, withdrawal of the rejections under 35 U.S.C. § 103(a) is respectfully requested.

CONCLUSION

In light of the above remarks, Applicants submit that the present application is fully in condition for allowance. Early notice to that effect is earnestly solicited.

If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, Applicants invite the Examiner to contact the undersigned.

The Commissioner is hereby authorized to charge any fees and credit any overpayment of fees which may be required under 37 C.F.R. §1.16, §1.17, or §1.21, to Deposit Account No. 18-1648.

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